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Dietary sodium as a risk factor for osteoporosis: where is the evidence?

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Na-induced calciuria has been well documented and provides a physiological basis for the proposed role of dietary Na (or salt) as a risk factor for osteoporosis. However, the evidence is based primarily on acute salt-loading studies, and there are insufficient data on the effects of high salt intake on net Ca retention to predict long-term effects on bone health. Results of investigations on salt and bone turnover, as assessed by bone biomarkers, are inconsistent, but the large variations in inter-individual response to acute and chronic Na loading may be related to salt sensitivity. Results of cross-sectional and prospective investigations on high salt intake and long-term bone health are inconclusive, probably reflecting the difficulty of conducting such studies in free-living populations. However, the mean urinary Ca loss of 1 mmol/100 mmol Na suggests that chronic changes in salt intake may have large effects on Ca and bone balance, especially in individuals with a reduced capacity to compensate for Na-induced Ca loss. Investigating the relationship between salt intake and bone health requires a greater focus on whole diets (including components such as K, Mg, P and protein), reliable measures of salt intake, appropriate bone health outcome measures, and improved subject characterisation (e.g. salt sensitivity). The reasons for inter-individual variability should be explored using post-genomic techniques.

Salt intake: Calcium metabolism: Calcium homeostasis: Bone health: Osteoporosis

It has been estimated that the Na intake from modern diets is about four times higher than that in pre-agricultural diets, and this increase has been primarily at the expense of K alkali salts (Frassetto *et al*. 2001). High salt intakes are linked to increased blood pressure, but salt also affects Ca metabolism and is, therefore, one of many purported risk factors associated with the development of osteoporosis. The current recommendation to reduce the average salt intake of the population to 6 g/d (Department of Health, 1994; Scientific Advisory Committee on Nutrition, 2003) is based entirely on the evidence of Na in relation to cardio-vascular disease, because 'there are insufficient data to assess effects of high salt intake on bone health and further research is required in this area' (Scientific Advisory Committee on Nutrition, 2003). Further characterisation of the relationship between Na and bone health is challenging because of the lack of sensitive short-term indicators of long-term bone health, coupled with a high level of background variability associated with heredity and environment. Other minerals, in particular K, as well as acid–base balance, affect the relationship between Na and Ca reabsorption in the kidney. This situation suggests that the role of salt as a risk factor for osteoporosis can only be further defined by investigating the effects of salt in the context of the overall diet, with particular reference to other dietary factors that affect Ca and bone economy, such as K and protein. The purpose of the present paper is to present a critical evaluation of current knowledge of dietary Na as a risk factor for osteoporosis and to discuss methodological challenges for future research.

Earlier reviews on salt and bone health

Several reviews examining the impact of Na on bone health have been published since 1990. Nordin *et al*. (1991) concluded that Na intake plays a very important role in determining the rate of obligatory Ca loss, and must, therefore, be a risk factor for osteoporosis. Massey & Whiting (1996) could find no evidence that the level of dietary Ca influenced salt-induced calciuria; nevertheless, they stated that it is reasonable to assume that a sufficiently high Ca intake will overcome loss of bone that occurs with a high salt intake. The authors emphasised the need to consider the effects of salt within the range of usual intakes, the anion effect, plus the influence of other nutrients such as protein, phosphate and K. Burger *et al*. (2000) reviewed the

Abbreviations: BMD, bone mineral density; PTH, parathyroid hormone.
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aetiology of osteoporosis, focusing on studies addressing the relationship between salt, Ca balance and bone metabolism. They concluded that the effect of salt intake on bone health remains controversial, and that data on fracture risk and salt intake are required to clarify the relationship between dietary salt and risk of osteoporosis. Shortt & Flynn (1990) highlighted inter-individual variation in Na-induced calciuria, which is possibly related to salt sensitivity, and the lack of information concerning the effect of salt loading on endogenous Ca secretion and Ca balance. They made an important point that has still to be resolved, i.e. that the increase in bone resorption observed with high salt intakes requires evidence of an effect on net bone loss before an association between Na intake and osteoporosis can be demonstrated.

Salt sensitivity

Individual differences in the blood pressure response to salt are probably explained by differences in genotype. Although salt sensitivity is a well-recognised phenomenon, there is no single definition (Weinberger, 1996), nor is its impact on Ca metabolism, and hence bone health, well understood. Wilson *et al*. (1996) defined salt sensitivity in two ways: (1) a decrease in mean blood pressure of ≥ 5 mmHg from baseline when consuming a low-Na diet; (2) an increase in mean blood pressure of ≥ 5 mmHg when moving from a low-Na to a high-salt diet.

Morris *et al*. (1999) defined salt sensitivity as an increase in mean arterial blood pressure of ≥ 3 mmHg with salt loading (250 mmol/d for 4 weeks), 'moderate' sensitivity as an increase in blood pressure of ≥ 10 mmHg, and the category 'severe' was applied when the response was any greater. They observed that salt-loading induced higher K losses in the urine, but when K supplements were given together with salt the blood pressure response was attenuated with 70 mmol K/d and abolished with 120 mmol K/d. The impact on urinary Ca excretion was similar; in fact, the highest K supplement resulted in a fall in urinary Ca excretion to a value lower than that measured with a low-salt diet. Clearly, salt, kidney function (Ca excretion) and blood pressure are metabolically interrelated, but the long-term impact of salt sensitivity on chronic diseases such as osteoporosis is not known. Weinberger *et al*. (2001) reported on a 30-year follow-up study in which they examined survival curves of 708 subjects (430 normal and 278 hypertensive), 44 % of whom were women. The survival rates for the normotensive salt-sensitive subjects were similar to those of the hypertensive subjects, whereas salt-resistant normotensive subjects had increased survival ($P < 0{\cdot}001$). Causes of death are not known for all subjects, nor are the mechanisms by which salt sensitivity may contribute to the mortality of normotensive subjects. Unfortunately, characterisation of subjects in terms of salt sensitivity is rarely, if ever, carried out in studies investigating the effect of salt on Ca metabolism or bone health. Thus, it is not possible at present to speculate on the effects of salt sensitivity on the risk of osteoporosis.

Urinary sodium, calciuria and calcium homeostasis

The kidney plays a key role in maintaining homeostasis of several mineral ions, particularly Ca, Na and K (Friedman, 2000); > 99 % of the Na and 95 % of the Ca are reabsorbed in the kidneys. Although not all mechanisms involved in Ca reabsorption are completely understood, there is agreement on the importance of the major transport mechanisms in the different segments of the nephron. The majority of Ca^{2+} (60–70 %) is reabsorbed along the proximal tubules via the paracellular route (passive reabsorption), which is governed by the extent of concomitant Na absorption. Passive Ca absorption also seems to be the major route of absorption in the ascending limb of Henlé's tube. In distal segments Ca^{2+} and Na^{+} transport are inversely related and under hormonal control, primarily parathyroid hormone (PTH), calcitonin and 1,25-dihydroxycholecalciferol. The reabsorption of Ca in the distal segments is tightly regulated and central to the maintenance of Ca homeostasis (Friedman, 2000). The recently-cloned apical epithelial Ca channel and the Ca-sensing receptor play a key role in the regulation of Ca transport (Reilly & Ellison, 2000).

In the absence of hydration disorders the quantity of Na in a 24 h urine specimen is almost the same as the quantity of Na ingested (Audran & Legrand, 2000). However, large fluctuations in daily Na intake require multiple 24 h urine collections for an accurate assessment of habitual Na intake (Shortt *et al*. 1988; Siani *et al*. 1989). Na-induced calciuria may result in hypercalciuria, defined as an excretion of > 0·1 mmol (4 mg)/kg per 24 h in urine. This excretion rate translates into a Ca excretion of > 7·5 mmol (300 mg)/kg per 24 h in males and 6·25 mmol (250 mg)/kg per 24 h in females (Coe *et al*. 1982). Martini *et al*. (2000) investigated high salt intake and its association with bone mineral density (BMD) in hypercalciuric stone-forming patients and calculated that a salt intake of > 16 g/d increases the risk of reduced bone density by 3·4-fold. Other researchers have supported the view that a high salt intake should be included in the list of factors causing and/or maintaining secondary hypercalciuria (Cirillo *et al*. 1997; Audran & Legrand, 2000).

The association between urinary Ca and Na in cross-sectional studies is consistent with the direct effect of changes in Na intake on urinary Ca observed in dietary intervention studies (Shortt & Flynn, 1990; Evans & Eastell, 1995; Massey & Whiting, 1996). However, the magnitude of the estimated increase in Ca excretion per 100 mmol rise in urinary Na can vary considerably (Shortt & Flynn, 1990; Massey & Whiting 1996); two-fold differences in the rise in urinary Ca at low (McCarron *et al*. 1981; Sabto *et al*. 1984) and high (Lietz *et al*. 1997; Sellmeyer *et al*. 2002) Na intakes are common. The conclusion from available data is that each 100 mmol (2300 mg) increase in 24 h urinary Na is associated with the loss of an additional 1·0 (range 0·5–1·5) mmol Ca/d in urine (Nordin *et al*. 1993; Massey & Whiting, 1996; Cohen & Roe, 2000). An additional daily urinary loss of approximately 40 mg Ca over 10 years may result in Ca losses equivalent to approximately 10 % of the total body Ca (Zarkadas *et al*. 1989), but adaptive mechanisms are present in the body to maintain Ca homeostasis.

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Na-induced calciuria temporarily depresses Ca^{2+} levels, setting in motion a series of events that aim to compensate for urinary Ca losses and restore normal serum Ca levels. The hypothesised sequence of events includes an increase in Ca reabsorption in the kidney and increased bone resorption mediated by increases in PTH secretion, and increases in Ca absorption from the gut in response to increased levels of 1,25-dihydroxycholecalciferol (Evans & Eastell, 1995). However, few studies have actually measured PTH in response to salt loading and results are inconsistent (McCarron *et al*. 1981; Breslau *et al*. 1982, 1985; Chan *et al*. 1992; Sellmeyer *et al*. 2002). Increases in PTH in response to salt loading in young adults, but not in post-menopausal women, have been interpreted as evidence for a lack of adaptation with increasing age (Breslau *et al*. 1985). Both Mg and P are involved in normal function of the parathyroid gland, hence they may affect adaptive responses to changes in Ca homeostasis (Zofkova & Kancheva, 1995). Vitamin D status also plays an important role in Ca metabolism, underlining the need to include measurements of vitamin D, PTH and other potential confounders when studying the effect of salt on bone health. There is also evidence to suggest that Ca absorption efficiency declines with age, which may be related to intestinal resistance to 1,25-dihydroxycholecalciferol (Pattanaungkul *et al*. 2000) and/or oestrogen loss (Heaney *et al*. 1989). The ability to compensate for Na-induced Ca loss may therefore depend on age and menopausal status.

Dietary modulators of sodium-induced calciuria

There is a paucity of data on the possible effects of dietary factors on Na-induced calciuria and/or their impact on Ca homeostasis at high and low salt intake. Key modulators include dietary P, protein (Lemann *et al*. 1979), K (Lemann *et al*. 1991*a,b*; Sellmeyer *et al*. 2002) and Mg (Zofkova & Kancheva, 1995). P and Mg (Calvo, 1994; Zofkova & Kancheva, 1995) may potentially modify Na-induced calciuria through their effect on calcitropic hormones, particularly via PTH, and subsequent effects on adaptive mechanisms. Depending on the accompanying anion and the level of dietary intake, K salts may modify the renal handling of Na and Ca, and thus need to be considered in dietary intervention trials studying the effect of Na on Ca and bone metabolism. It has been suggested that the K effect is the result of two mechanisms working synergistically. K-induced Na and chloride excretion that reduces extracellular volume expansion may be responsible for reduced Ca excretion, while the concomitant reduction in net acid excretion has been shown to be independently associated with reduced Ca excretion (Lemann *et al*. 1991*a,b*; Sebastian *et al*. 1994; Morris *et al*. 1999). Based on a series of experiments Lemann *et al*. (1993) estimated that an additional dietary 20 mmol (780 mg) $KHCO_3$/d could reduce Ca excretion by 0·3 mmol (12 mg)/d. Supplementation with 90 mmol (3510 mg) potassium citrate/d prevented an increase in urinary Ca induced by a high salt intake (13 g salt) over a 4-week period. This quantity of additional K would correspond to a doubling of the current intake of K in the ≥ 65 years age-group in the UK (Finch *et al*. 1998). The high extent of inter-correlation amongst these nutrients complicates the interpretation of independent dietary associations, and may also contribute to the frequently observed inter-individual variation in the Na-induced Ca losses.

Inter-individual variation, ethnic origin and skeletal maturity

In controlled salt-loading studies of small sample size with various Na loads and Ca intake levels the response to Na-induced calciuria has been reported to range widely, from reduced Ca excretion to a several-fold increase in urinary Ca losses (Kirkendall *et al*. 1976; Castenmiller *et al*. 1985; Shortt *et al*. 1988; Ginty *et al*. 1998). Whether the observed inter-individual differences in the extent of the response are partly related to salt sensitivity and/or other dietary confounders remains to be established. However, the effect should be considered when calculating study sample size to ensure statistical power of the outcome measures.

Prevalence of salt sensitivity in the population is not well defined, but prevalence is estimated at 25 % for a normotensive population (Scientific Advisory Committee on Nutrition, 2003). The literature further suggests that salt sensitivity in normotensive individuals is more frequent in blacks than in whites, but only when K intakes are low or deficient (Morris *et al*. 1999). Results from the Wandsworth Heart and Stroke study (Blackwood *et al*. 2001) investigating urinary Ca excretion, Na intake and blood pressure in a multi-ethnic population suggest that blood pressure, salt intake and ethnic origin are independent predictors of urinary Ca. Differences between white and black female adolescents in their response to high-Na diets have also been reported (Palacios *et al*. 2001). On high-Na diets (4·0 g Na/d) fed over a 3-week period black girls had a higher positive Na balance, lower aldosterone levels and suppressed plasma rennin activity, suggesting renal Na retention. There is also evidence that Ca and Na excretion in response to salt and/or K interventions is different in younger populations. In an acute short-term load test in prepubescent girls K increased Na excretion and reduced net acid excretion but had no effect on Ca excretion (Duff & Whiting, 1998), whereas in adults the K treatment resulted in marked hypocalciuria (Whiting *et al*. 1997). These findings suggest that state of skeletal maturity and ethnic origin are independent predictors for different dietary requirements at any given Na intake.

Assessment of sodium as a risk factor for osteoporosis according to outcome measure

Different outcome variables can be used to assess the effect of dietary salt on Ca and bone metabolism. The majority of investigations are short-term because of the practical and logistic difficulties involved with long-term observational or intervention studies. They are usually designed to assess the effects of various salt intakes on Ca homeostasis and/or bone turnover. However, changes in BMD or bone mass and/or fracture risk are considered to be the gold standard for establishing a significant long-term effect on bone health. The evidence of salt as a risk factor for osteoporosis will be summarised in the following sections according to outcome measure.

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Calcium absorption

Na-induced calciuria may initiate changes in the efficiency of dietary Ca absorption in an attempt to maintain Ca balance. With a mean daily intake of 700 mg Ca, a 5 % increase in absorption efficiency would provide an additional 40 mg Ca, thereby compensating for the mean calciuric effect of Na. If the efficiency of absorption remains unchanged then Ca intake would need to increase by 150 mg to compensate for the Na-induced Ca loss. An individual's capacity to conserve Ca at low Ca intakes is very variable and associated with a persistent PTH response (Barger-Lux & Heaney, 1993). Hence, evidence for compensatory increases in Ca absorption is an important determinant of the overall risk of salt for osteoporosis. However, only a small number of dietary intervention studies (Meyer *et al*. 1976; Breslau *et al*. 1982, 1985; McParland *et al*. 1989; Evans *et al*. 1997) and one cross-sectional study (Cirillo *et al*. 1997) have actually investigated the effect of low and high Na intake on Ca absorption efficiency. A summary of these studies is given in Table 1. Na-induced calciuria was a common characteristic, but was only associated with an increase in Ca absorption (of approximately 16 %) in two (Meyer *et al*. 1976; Breslau *et al*. 1982) of five salt-loading studies (Table 1). The lack of consistency is almost certainly a result of differences in subject characteristics (and small numbers), methodologies employed and the difference between the low and high salt intake within each study. In particular, the use of a less-sensitive Sr test (McParland *et al*. 1989; Evans *et al*. 1997) as a surrogate measure of Ca absorption is not ideal (Reynolds & Smith, 1994; Blumsohn & Eastell, 1995). The results of the only cross-sectional study (Cirillo *et al*. 1997) showed no significant correlation between Ca absorption efficiency and 24 h urinary Na excretion, but the numbers of subjects were rather small for a cross-sectional study and would have provided limited statistical power. Changes in endogenous secretion of Ca into the intestinal lumen (Heaney & Recker, 1994) have not been investigated in response to salt loading. There is also evidence to suggest that adaptation periods of < 14 d, as employed in these studies, are probably too short for homeostatic mechanisms to reach a new equilibrium (Roughead *et al*. 2003). The results of the three intervention studies using ^{47}Ca-absorption techniques suggest that the efficiency of Ca absorption may increase in non-osteoporotic individuals in response to high-salt diets. However, to date there are insufficient data to confirm or characterise fully any adaptive response to Na-induced calciuria.

Salt intake and bone turnover

Bone loss is due to an imbalance between the rates of bone formation and bone resorption, reduced bone formation, increased bone resorption or a combination of these factors. The literature in this area suggests that nutritional factors that affect bone resorption are easier to identify than those that may affect bone formation. The evidence considered in this section will include studies based on bone resorption markers other than hydroxyproline, which is no longer considered a reliable marker of bone resorption (Seibel & Woitge, 1999). A cross-sectional study of 154 Australian subjects (20–70 years of age) showed a weak but significant positive correlation (r 0·32, $P < 0·0001$) between Na and deoxypyridinoline excretion (Jones *et al*. 1997). Itoh *et al*. (1999) found a positive correlation (r 0·167; $P < 0·05$) between deoxypyridinoline and Na intake in 216 Japanese women aged 50–79 years only, which suggests that this age-group may be at higher risk because of a decreased ability to compensate for Na-induced Ca losses. Both studies determined Na intake by 24 h urine analysis (considered to be a robust and reliable measure), whereas New *et al*. (2000), who did not find any correlation between Na intake and deoxypyridinoline excretion in a cross-sectional study of sixty-two women aged 45–55 years, used a food-frequency questionnaire. In the latter study, however, other dietary factors, including Mg (r –0·37; $P < 0·005$) and K (r –0·31; $P < 0·01$), were shown to be inversely related to urinary deoxypyridinoline excretion. One of the major

Table 1. Salt intake and efficiency of calcium absorption

	Subjects		Age (years)						
Reference	*n*	Gender	Mean	SD	Na intake (g/d)	Ca intake (mg/d)†	Metabolic period (d)	Technique	Increase in Ca absorption (%)
Meyer *et al*. (1976)	6	M and F	*		Low: 0·2	600	12	^{47}Ca§	16·5 ($P < 0·0005$)
					High: 5·7	600	12		
Breslau *et al*. (1982)	11	M and F	22–36		Low: 0·2	400	10	^{47}Ca‖	16·0 ($P < 0·01$)
					High: 5·7	400	10		
Breslau *et al*. (1985)	7 (osteoporotic)	F	67	8	Low: 0·2	400	10	^{47}Ca‖	NS ($P > 0·05$)
					High: 5·7	400	10		
McParland *et al*. (1989)	10	F	66·8	1·3	Low: 1·6	850	10	Sr¶	NS ($P > 0·05$)
					High: 3·9	850	10		
Evans *et al*. (1997)	11	F	32	8·9	Low: 1·2	861‡	7	Sr¶	NS ($P = 0·922$)
	11	F	57	8·1	High: 6·9	741‡	7		NS ($P = 0·874$)
Cirillo *et al*. (1997)	36	M and F	18–65		4209 (SD 1909)	Habitual	Cross-sectional	Sr¶	NS ($P > 0·05$)

*Not reported.
†Diet controlled for Ca intake, except where indicated otherwise.
‡Habitual intake.
§Single-radioisotope-tracer method based on external radioisotope counting in the forearm.
‖Single-radioisotope-tracer method based on faecal monitoring.
¶Single-stable-isotope method based on serum Sr concentration.

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limitations of cross-sectional studies is inappropriate assessment of Na intake (e.g. food-frequency questionnaire) or length of assessment (a single 24 h urine), and also the lack of control for other dietary factors known to affect Na and/or Ca excretion.

Controlled longitudinal dietary intervention studies (as summarised in Table 2) are the preferred means of generating evidence for the effect of high Na intake on bone turnover at various Ca intake levels. However, results to date can, at best, be described as inconsistent. This inconsistency may be a result of differences in salt and Ca levels tested and short metabolic periods (< 14 d), which may not be long enough to allow for the completion of one bone resorption cycle (Mundy, 1999). The most-recently published study (Sellmeyer *et al*. 2002) is a marked improvement on previous studies in two important aspects, i.e. length of intervention and number of subjects. Sellmeyer *et al*. (2002) studied two groups of post-menopausal women at low (2000 mg/d) and high (5175 mg/d) Na intakes with the addition of either a placebo or a potassium citrate supplement during the high-salt intervention. The high-Na diet resulted in calciuria and significantly ($P = 0{\cdot}001$) increased (by 23 %) the bone resorption marker, cross-linked N-telopeptides, in the placebo group. The addition of potassium citrate prevented Na-induced calciuria and the cross-linked N-telopeptide level was unchanged compared with the low-salt diet ($P = 0{\cdot}3$) and significantly lower compared with the placebo group ($P = 0{\cdot}049$). It is noteworthy that the Ca excretion (mean 200 mg) on the low-salt diet (2000 mg Na/d) was similar to the baseline assessment (mean 215 mg for placebo group and 201 mg for potassium citrate group) during which volunteers consumed their habitual diet containing an average of 3312 mg Na/d. This finding suggests that there was no further reduction in Ca excretion when Na intake was reduced from 3312 mg/d (equivalent to 8·4 g salt/d) to 2000 mg/d (equivalent to 5 g salt/d). Na restriction has been shown to reduce the intake of other nutrients, including Ca (Morris, 1997), but this study did not report habitual Ca at baseline or during the low-salt intervention. There was no significant increase in urinary Ca excretion on the low-Na diet compared with baseline, although volunteers were supplemented with 500 mg Ca during the intervention. This finding indicates that the volunteers had a habitual high Ca intake and/or were in negative Ca balance and may, therefore, have incorporated the additional retained Ca into bone tissue.

The findings of Sellmeyer *et al*. (2002) and New *et al*. (2000) underline the importance of characterising the whole diet with regard to the renal handling of Na and Ca. Preliminary results from the Dietary Approaches to Stop Hypertension trial suggest that the experimental diet (high in fruit, vegetables and wholegrain foods) is effective in reducing bone turnover at all levels of salt intake. There appeared to be no effect of salt on bone biomarkers in the control group at low, medium or high salt intakes (Lin *et al*. 2001). Although the evidence so far is too inconsistent to conclude that a high Na intake increases bone resorption, it has become clear that Na cannot be studied in isolation from other dietary modulators such as K and protein. This area of research would benefit from more rigorous study designs that permit longer adaptation periods.

Salt intake and bone mineral density or fracture risk

As lengthy periods of investigation (> 1 year) are required to determine the effect of salt intake on BMD, the evidence is mostly based on observational data rather than longitudinal interventions. A cross-sectional analysis of 105 Danish

Table 2. Summary of studies investigating the effect of salt loading on bone biomarkers

Reference	Subjects			Ca (mg/d)	Na (mg/d)	Intervention period (d)	Change in bone biomarker
	n	Gender	Mean age (years)				
McParland *et al*. (1989)	9	F	66·8	850*	Low: 1610 High: 3910	10	OC: NS ($P = 0{\cdot}05$)
Lietz *et al*. (1997)	14	F	62·3	816*	Low: 1380 High: 3910	8	Dpyr: NS ($P > 0{\cdot}05$) Pyr: NS ($P > 0{\cdot}05$)
	11	F	57	741 (habitual)	Low: 1150 High: 6900	7	Dpyr: 21 % increase on high-salt diet ($P = 0{\cdot}024$) OC: NS ($P > 0{\cdot}05$)
Evans *et al*. (1997)	11	F	32	861 (habitual)	Low: 1150 High: 6900	7	Dpyr: NS ($P > 0{\cdot}05$) OC: 8 % decrease on high-salt diet ($P = 0{\cdot}024$)
	8	F; Na-sensitive	22·1	500*	Low: 1840 High: 4140	14	Dpyr:NS ($P > 0{\cdot}05$) Pyr: NS ($P > 0{\cdot}05$) OC: NS ($P > 0{\cdot}05$)
Ginty *et al*. (1998)	8	F; Na non-sensitive	23·3	500*	Low: 1840 High: 4140	14	Dpyr: NS ($P > 0{\cdot}05$) Pyr: NS ($P > 0{\cdot}05$) OC: NS ($P > 0{\cdot}05$)
Sellmeyer *et al*. (2002)	26	F	63·8	Habitual + 500	Low: 2000 High: 5170	28	NTx: 23 % increase on high-salt diet ($P = 0{\cdot}001$) OC: 5 % decrease on high-salt diet ($P = 0{\cdot}01$)

OC osteocalcin; Dpyr, deoxypyridinoline; Pyr, pyridinoline; NTx, N-terminal telopeptide.
*Diet controlled for Ca intake

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children (aged 10 years) reported a negative association between size-adjusted bone area and intakes of Na ($P = 0{\cdot}048$) and P ($P = 0{\cdot}01$; Hoppe *et al*. 2000). In contrast, other researchers did not find a significant inverse relationship between Na intake and BMD in children or adolescent girls (Matkovic *et al*. 1995; Jones *et al*. 2001). However, in agreement with studies already discussed, Na intake was the main determinant of urinary Ca in adolescent girls (Matkovic *et al*. 1995). Matkovic *et al*. (1995) concluded that a high dietary salt intake during the growth spurt could compromise Ca balance in those with low Ca intakes. The lack of association between Na intake and BMD may be due to regression dilution bias, which may only be avoided by repeated measures of both urinary Na and bone mass in combination with a longitudinal study design.

In free-living adults and post-menopausal women there is currently no evidence that salt intake and BMD are inversely related (Greendale *et al*. 1994; Reid *et al*. 1994; Dawson-Hughes *et al*. 1996; Jones *et al*. 1997). However, with all epidemiological investigations there are well-known problems surrounding the collection of dietary information, including Na intake. Greendale *et al*. (1994) carried out a 16-year prospective cohort study in 258 women (mean age 73·3 years) and 169 men (mean age 72·4 years) and found no association between Na intake and BMD. However, the assessment of Na intake was inadequate, being based on a single 24 h dietary recall at baseline; thus, the results of this study are unreliable. In another prospective study Na intake (2430 (SD 676) mg/d) was determined in 122 post-menopausal women by a 4 d diet diary at baseline (Reid *et al*. 1994). At the end of the 2-year study it was not found to be a significant determinant of bone loss, but the renal tubular reabsorption of Ca was shown to be inversely related to the change in BMD in the trochanter.

In the literature there seem to be only two controlled intervention studies that have investigated the relationship between salt intake and BMD. Nordin & Polley (1987) undertook a 9-month intervention trial in post-menopausal women in which various dietary treatments were examined, including salt restriction. Unfortunately, the results are difficult to interpret because the control group, unexpectedly, had a reduced rate of bone loss during the study period, possibly due to a change in dietary pattern initiated by the publicity surrounding the study. Women with high Ca intakes who were salt restricted exhibited a very significant ($P < 0{\cdot}005$) fall in the rate of bone loss. The authors proposed that salt restriction might be a more effective measure in individuals on low Ca intakes, although there is no evidence to substantiate this hypothesis. Devine *et al*. (1995) carried out a 24-month intervention of Ca supplementation and/or an exercise programme in a total of 124 post-menopausal women without changing Na intake. They found that a high Na intake was associated with increased bone loss at the hip but not spine (r −0·192). The lack of effect at the spine site may have been due to confounding effects of degenerative joint disease or aortic calcification prevalent in this age-group. Regression equations for Na excretion and change in bone density at the total hip site showed that halving urinary Na excretion from 3450 mg (equivalent to 8·8 g salt)/d to 1725 mg (equivalent to 4·4 g salt)/d would have an effect on bone density equivalent to an increase in daily dietary Ca of 891 mg, which suggests a potentially powerful effect of Na on bone loss at the hip.

The overall evidence from cross-sectional and longitudinal prospective studies on salt reduction and BMD is inconsistent and not helped by the lack of long-term randomised controlled trials. Future research needs to take into account the large errors associated with the assessment of Na intake by any means other than urinary Na excretion. There appears to be no published data on the relationship between Na intake and fracture risk.

Summary

The evidence for a detrimental effect of high salt intake on bone health is primarily limited to short-term effects of Na on Ca metabolism. The literature provides strong evidence for a calciuretic effect with high salt intake, but the extent to which variations in salt intake, within the range commonly observed, might influence the maintenance of bone mass is not clear. This situation is the result of a lack of well-designed long-term investigations on salt intake in relation to BMD and fracture risk. In the absence of such data the focus should be investigating the extent to which Na-induced calciuria can be compensated by changes in the efficiency of Ca absorption, and whether this process depends on Ca intake and other dietary modulators such as K and protein. Cross-over design studies that use sensitive measures of Ca absorption, appropriate adaptation periods and include determinations of calcitropic hormones are required. There is a need for more rigorous study designs that will allow the determination of the effect of salt intake on bone turnover. The interpretation of the outcome of these studies will also depend on the concomitant assessment of the main dietary modulators that affect the relationship between Ca and Na.

While some researchers may consider the well-documented calciuretic effects as merely circumstantial evidence for a detrimental effect of high salt intake on bone health, others argue that the consistency of the evidence is sufficient to support a recommendation of lower salt intake at a population level (Cappuccio, 2001). The most recent public health advice in the UK is to reduce salt intake from an average of 9 g/d to 6 g/d, and a concerted effort has been initiated through a government–food industry partnership to reduce the salt intake of the population in processed foods (Food Standards Agency, 2003). This initiative will provide an opportunity to establish whether the recommended reduction in salt intake benefits Ca and bone metabolism. Although the previous focus has been on post-menopausal women, there is a pressing need to characterise the role of Na and K in the context of the whole diet during the growth phase. It is imperative that there is a better understanding of the complex interplay between salt and other dietary modulators of Ca metabolism to provide better informed guidelines for optimal skeletal health.

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